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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
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ART UNIT	PAPER NUMBER
1636	14

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/830,669	MARLIERE ET AL.	
	Examiner	Art Unit	
	Gerald G Leffers Jr.	1636	

-- The MAILING DATE of this communication appears on the c ver sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *02 January 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disp sition of Claims

4)☒ Claim(s) *1-51* is/are pending in the application.

4a) Of the above claim(s) *35-51* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-34* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *1* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

Receipt is acknowledged of a response (filed on 1/2/03 as Paper No. 13) to the Notice to Comply mailed 12/3/02 as Paper No. 10. The amendments have been entered into the specification and the application is now in sequence compliance.

Election/Restrictions

Applicant's election with traverse of Group I (claims 1-14, 18) in Paper No. 9, filed 9/23/02, is acknowledged. The traversal is on the ground(s) that 1) the claims of the other groups are dependent on claims within Group I and are thus not restrictable from the claims of Group I; 2) the groups were not restricted from one another in the preliminary examination provided by the Preliminary Examination Authority; 3) PCT Article 27 states that no national law shall require compliance with requirements relating to the form and contents of the International application different from or additional to those which are provided for in the Patent Cooperation Treaty and the Regulations; and 4) MPEP 803 states that if the search can be made without a serious search burden the Examiner must examine all claims, even if drawn to distinct and independent inventions and that doing so in the instant application would not require a burdensome search. This is not found entirely persuasive because of the following reasons.

It is in fact permissible to restrict dependent claims from independent claims if it can be shown that the special technical feature of the dependent claim is not the same as that of the independent claim. In the instant case, the special technical feature of the invention is the use of special growth conditions to select for mutant cells that have acquired the ability express an essential protein that comprises a missense mutation. Because the instant specification only exemplifies this embodiment wherein mutant forms of aminoacyl-tRNA synthetase are

generated, and because these embodiments are the special technical feature given in the restriction requirement for Group II (claims 15-17, 19-34), the claims of Group II are hereby rejoined with those of Group I.

The argument that the claims were not restricted by the Preliminary Examination Authority does not carry significant weight because restriction can occur at any time during examination of an application. With respect to the argument that no national law shall require compliance with regulations different from those of the PCT, the examiner at no time attempted to use U.S. restriction practice in making the requirement. On the contrary, the restriction was made as per the PCT guidelines for lack of Unity of Invention. Accordingly, applicants' arguments concerning no serious search burden are not applicable for the instant specification. Applicants have presented no arguments as to the examiner's rational as to why the inventions lack Unity of Invention.

The requirement is still deemed proper for Groups III-V and is therefore made FINAL. Claims 1-51 are pending in the instant application, with claims 35-51 withdrawn from consideration as being directed to nonelected inventions. Claims 1-34 are under consideration.

Information Disclosure Statement

Receipt is acknowledged of an IDS filed 8/29/01. The signed and initialed PTO Form 1449 has been mailed along with this action.

Claim Objections

Claims 1-34 are objected to because of the following informalities: the claims frequently refer to steps of the claimed methods in the body of the claims with only a single parenthesis around the letter corresponding to that step (e.g. "...the protein of step a) wherein the codon..."). In order to clarify the claim language it would be desirable to amend the claims so that the reference letters are enclosed within two parentheses (e.g. "...the protein of step (a) wherein the codon..."). Appropriate correction is required.

Claims 1-34 are objected to because of the following informalities: the claims are not written as a single sentence. It would be remedial to 1) amend the claims section to read "We claim:", and 2) to insert an article at the beginning of each claim (e.g. "The" or "A"). Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1, 3-34 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for embodiments where the target cells are grown in selective conditions where the culture medium 1) does not comprise the nutrient required by the loss of functionality of the mutated protein of step (a), and 2) further comprises the amino acid encoded by the target codon prior to its alteration in step (a) , does not reasonably provide enablement for embodiments lacking this specific selection step. The specification does not enable any person

skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Enablement is considered in view of the Wands factors (MPEP 2164.01(A)). These include: nature of the invention, breadth of the claims, guidance of the specification, the existence of working examples, state of the art, predictability of the art and the amount of experimentation necessary. All of the Wands factors have been considered with regard to the instant claims, with the most relevant factors discussed below.

The nature of the invention is complex, involving the use of selection pressures to select cells comprising a mutation that allow the cell to incorporate unconventional amino acids. The claimed methods utilize a missense mutation in a gene encoding an essential protein for a target cell to select for cells that acquire the ability to compensate for the loss of the function of the essential protein. The claims encompass embodiments where such selection pressure is not applied. The specification describes experiments where cells modified to include missense mutations in an essential gene are grown in defined media (e.g. minimal media) in the presence of large quantities of an amino acid encoded by the original target codon of the essential protein (i.e. prior to the incorporation of the missense mutation), where the selective media does not comprise a nutrient whose requirement is necessitated by the missense mutation of the essential protein. The working examples are solely directed to embodiments where selective pressure is applied by culturing in defined media 1) lacking a nutrient required by the mutation of the essential protein, and 2) in the presence of the amino acid encoded by the target codon prior to its alteration to a missense codon. In each of the working examples, applicants were able to demonstrate a mutation in the aminoacyl-tRNA synthetase corresponding to the missense codon

which allows the mutated aminoacyl-tRNA synthetase to incorporate amino acids other than the one specified by the missense codon (e.g. the amino acid encoded by the original target codon or other, non-canonical amino acids such as aminobutyrate). The specification teaches two working examples wherein the mutated aminoacyl-tRNA synthetase obtained via their selection methods apparently has increased ability to incorporate non-canonical amino acids such as L-2-aminobutyrate or L-3-thiol-2-aminobutyrate (e.g. Examples 6-7). However, no teachings or working examples are provided for embodiments lacking this selection pressure. No rational is provided for how one would expect to obtain mutants allowing incorporation of such unconventional amino acids in the absence of the cited selection pressure (i.e. absence of the required nutrient and presence of the original amino acid).

The methods described in the specification appear to be novel in the art. Therefore, there is no teaching in the prior art to offset the cited deficiencies of the instant specification. Because no rational is provided in the instant specification or prior art for practicing embodiments of the claimed invention in the absence of selection pressure applied by culturing the cells in the presence of the amino acid encoded by the original target codon and in the absence of the essential nutrient necessitated by alteration of the target codon, it would be unpredictable to attempt to practice the claimed methods in the absence of such selection pressure. Therefore, it would take undue, trial-and-error experimentation of an unpredictable nature to practice the claimed methods in the full broad scope encompassed by the rejected claims.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-34 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1 is vague and indefinite in that the metes and bounds of the phrase "Method which allows cells to acquire the capacity to produce a protein....which comprises at least one unconventional amino acid..." are unclear. Does the term "allows" mean that the cell necessarily acquires the recited capacity? Or can one successfully practice the claimed invention if the cell does not actually acquire the recited capacity? Upon reading the specification, it appears the method is one wherein cells are grown under selective conditions such that the cell necessarily acquires a mutation allowing it to produce a polypeptide having an unconventional amino acid.

Claim 1 recites the limitation of "at least one unconventional amino acid". The specification defines the term as encompassing "...any amino acid incorporated in place of the amino acid which should normally be incorporated at this site with regard to the translated nucleic acid sequence...". It is unclear how one would determine if an amino acid is "normally" part of the protein? It is noted that the term "unconventional amino acid" is not directly linked to the missense codon of part (a) and that the protein in the preamble of the claim is not necessarily the essential protein of step (a) that comprises the missense mutation. The term protein in the preamble could apply to any protein one might wish to express in the cell obtained by the claimed methods. Again, how does one determine for such a protein whether it comprises an amino acid that is not "normally" part of the protein?

Claim 1 is further vague and indefinite in that the meets and bounds of the phrase "transforming said cells" are unclear. The cited phrase implies an additional step that is not necessarily present in the claims. Normally, the process of "transforming" cells refers to either immortalizing eukaryotic cells or introducing recombinant nucleic acids into microbial cells, and not simply introducing a missense mutation into an essential gene. It would be remedial to simply delete the phrase from the claim and have the claim recite something like "introducing at least one missense mutation".

Claim 1 is further vague and indefinite in that the metes and bounds of the term "where appropriate" are inherently subjective. It appears that applicants intend the limitation to be "optionally" culturing the cells obtained in step (a) in a culture medium containing a nutrient compensating for the loss of the function of the essential protein of step (a).

Claim 1 is also vague and indefinite in that there is no clear and positive prior antecedent basis for the term "said target codon" in part (c) of the claim. Does the term refer to the target codon before or after incorporation of the missense mutation? For example, the term could be interpreted as referring to a codon position within the coding sequence rather than to a particular codon sequence. Upon reading the specification, it appears it would be remedial to modify the claim language to more clearly indicate that the term refers to the amino acid specified by the target codon prior to its alteration.

Claim 3 is vague and indefinite in that the metes and bounds of the term "series of said cells" are unclear. It is unclear what a "series" encompasses. It would be remedial to amend the claim to more clearly indicate what is intended by a "series" of cells. Upon reading the specification, it appears claim 3 may be intended to specify a series of cultivation steps of the

same cells under selective conditions until mutants capable of growing in the absence of the nutrient required by loss of the functionality of the mutated protein.

In claim 5, the use of the words "preferably three bases" is inherently indefinite in that it is unclear whether the limitation must be three bases or can be two bases. It would be remedial to amend the claim to indicate the change can be of at least two bases (i.e. the target codon comprises at most three bases).

In claim 6, the term "small steric volume" makes the claim indefinite. The term is not explicitly defined in the specification and is inherently subjective.

Likewise, the term "substantially equal" in claim 8 is inherently subjective and is not clearly defined in the specification.

Claim 13 is vague and indefinite in that the metes and bounds of the term "where appropriate" are inherently subjective. It appears that applicants intend the limitation to be "optionally" culturing the cells obtained in step (a) in a culture medium containing a nutrient compensating for the loss of the function of the essential protein of step (a).

Claim 14 is vague and indefinite in that there is no clear and positive prior antecedent basis for the term "said target codon" in the claims upon which claim 14 is dependent. Does the term refer to the target codon before or after its alteration? Also, the use of the term "possibly being" is indefinite.

Claims 15 and 19 recite the limitation of "at least one unconventional amino acid". The specification defines the term as encompassing "...any amino acid incorporated in place of the amino acid which should normally be incorporated at this site with regard to the translated nucleic acid sequence...". It is unclear how one would determine if an amino acid is "normally"

part of the protein? It is noted that the term "unconventional amino acid" is not directly linked to the missense codon of part (a) and that the protein in the preamble of the claim is not necessarily the essential protein of step (a) that comprises the missense mutation. The term could apply to any protein one might wish to express in the cell obtained by the claimed methods. Again, how does one determine for such a protein whether it comprises an amino acid that is not "normally" part of the protein?

Claim 17 is vague and indefinite in that there is no clear and positive prior antecedent basis for the term "said mutation" in the claims upon which claim 17 is dependent. The term could be applied to the missense mutation of part (a) or to the mutation in the aminoacyl-tRNA synthetase.

Claim 20 is vague and indefinite in that it is unclear how the cell of claim 18 could be other than a prokaryotic or eukaryotic cell.

Claims 23-24 provide for the use of methods or cells, but, since the claim does not set forth any steps involved in the method/process, it is unclear what method/process applicant is intending to encompass. A claim is indefinite where it merely recites a use without any active, positive steps delimiting how this use is actually practiced.

Claims 23-24 are rejected under 35 U.S.C. 101 because the claimed recitation of a use, without setting forth any steps involved in the process, results in an improper definition of a process, i.e., results in a claim which is not a proper process claim under 35 U.S.C. 101. See for example *Ex parte Dunki*, 153 USPQ 678 (Bd.App. 1967) and *Clinical Products, Ltd.* v. *Brenner*, 255 F. Supp. 131, 149 USPQ 475 (D.D.C. 1966).

Claim 25 is vague and indefinite in that there is no clear and positive prior antecedent basis for the phrase "from the cell pellet obtained in step b)" in step (b) of the claim.

Claim 30 is vague and indefinite in that the metes and bounds of the term "target codon" are unclear. Does the use of the term in claim 30 mean that the target codon of the gene of interest is the same as that in part (a) of the process, or can it be a different target codon?

Claim 32 is vague and indefinite in that it is unclear what is encompassed by the concept of a "partially conserved" biological activity. The concept is not clearly explained in the specification and is indefinite.

Claim 33 is vague and indefinite in that the metes and bounds of the phrase "functional group capable of reacting selectively" are unclear because it is not specified as to what the functional groups are selectively reacted.

Conclusion

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Gerald G Leffers Jr. whose telephone number is (703) 308-6232. The examiner can normally be reached on 9:30am-6:00pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Remy Yucel can be reached on (703) 305-1998. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 305-7939 for regular communications and (703) 305-7939 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

Gerald G Leffers Jr.
Examiner
Art Unit 1636

Ggl
March 23, 2003